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(71) Applicants (for all designated States except US):
NOVIRIO PHARMACEUTICALS LIMITED [—/—];
Walker Secretaries, Walker House, Grand Cayman (KY).

UNIVERSITA DEGLI STUDI DI CAGLIARI [IT/IT];
Dip. Biologia Sperimentale, Sezione di Microbiologia,
Citadella Universitaria SS 554, Km. 4.500, I-09042
Monerrato (IT).

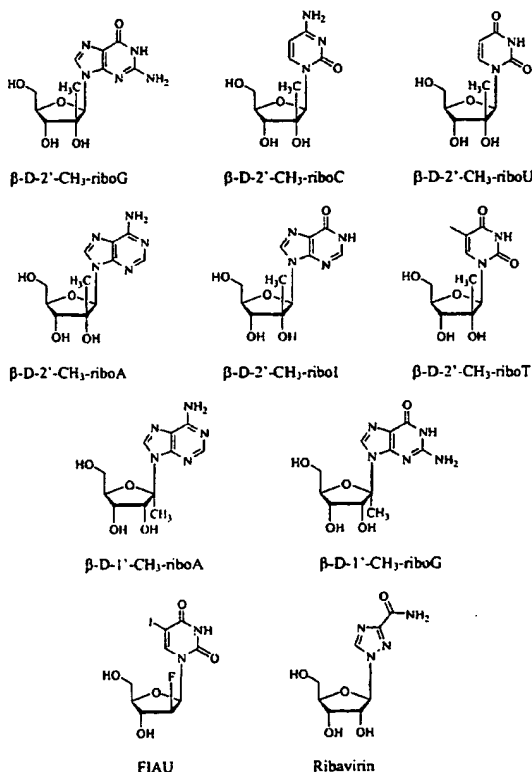
(72) Inventors; and
(75) Inventors/Applicants (for US only): SOMMADOSSI,
Jean-Pierre [FR/US]; 5075 Greystone Way, Birmingham,
AL 35242 (US). LACOLLA, Paolo [IT/IT]; 5 Strada no.
11, Poggio dei Pini, I-09012 Capoterra (IT).

(74) Agent: KNOWLES, Sherry, M.; King & Spalding, 191
Peachtree Street, Atlanta, GA 30303-1763 (US).

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR TREATING FLAVIVIRUSES AND PESTIVIRUSES



(57) Abstract: A method and composition for treating a host infected with flavivirus or pestivirus comprising administering an effective flavivirus or pestivirus treatment amount of a described 1', 2' or 3'-modified nucleoside or a pharmaceutically acceptable salt or prodrug thereof, is provided.



MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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2 May 2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/16687

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/06 C07H19/10 C07H19/16 C07H19/20 A61K31/7068
A61K31/7076 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|---|
| Y | <p>US 5 977 325 A (EDWARDS MICHAEL L ET AL) 2 November 1999 (1999-11-02)</p> <p>column 2, structure 1b column 23, lines 11-27 column 26, lines 5-10 the whole document</p> <p>----</p> <p>-/-</p> | <p>25, 28-39, 52-63, 76, 79-90, 103-114, 127, 130-141, 154-165, 178</p> |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 February 2002

Date of mailing of the international search report

04.03.2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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Int: tional Application No

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | X. MARTIN ET AL.: "Intramolecular hydrogen bonding in primary hydroxyl of thymine 1-(1-deoxy-beta-D-psicofuranosyl) nucleoside" TETRAHEDRON, vol. 50, 1994, pages 6689-6694, XP002176339 | 4,7,10, 23 |
| Y | page 6689, introduction figure 1 | 25,28, 31,34, 37,52, 55,58, 61,76, 79,82, 85,88, 103,106, 109,112, 127,130, 133,136, 139,154, 157,160, 163,178 |
| X | --- E. ROGERS ET AL.: "2'C-alkylribonucleosides: design, synthesis, and conformation" NUCLEOSIDES & NUCLEOTIDES, vol. 16, 1997, pages 1457-1460, XP002189347 | 2,5,8, 11,20, 22-24 |
| Y | compounds 8a-f page 1457, paragraph 1 | 25,29, 32,35, 38,53, 56,59, 62,76, 80,83, 86,89, 104,107, 110,113, 127,131, 134,137, 140,155, 158,161, 164,178 |
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| X Y | GB 1 209 654 A (MERCK & CO INC) 21 October 1970 (1970-10-21) page 2 lines 17-19 the whole document | 5,6,8,9, 11,12 25,30, 33,36, 39,54, 57,60, 63,76, 81,84, 87,90, 105,108, 111,114, 127,132, 135,138, 141,156, 159,162, 165,178 |
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| X | --- P. FRANCHETTI ET AL.: "2'-C-Methyl analogues of selective adenosine receptor agonists: Synthesis and binding studies" J. MED. CHEM., vol. 41, 1998, pages 1708-1715, XP002189348 compounds 4-9,12,13 --- -/-- | 2,8,11, 20 |

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| X | FR 1 521 076 A (MERCK & CO INC) 12 April 1968 (1968-04-12) the whole document | 2,8,11 |
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| X | --- L.N. BEIGELMAN ET AL. : "Epimerization during acetolysis of 3-O-acetyl-5-O-benzoyl-1,2-O-isopropyliden e-3-C-methyl-alfa-D-ribofuranose." CARBOHYDRATE RESEARCH, vol. 181, 1988, pages 77-88, XP002189350 compounds 13-15 | 3,6,9,12 |
| X | --- H. HREBACEKY ET AL.: "Nucleic acid components and their analogues. CXLIX. Synthesis of pyrimidine nucleosides derived from 1-deoxy-D-psicose" COLLECTION CZECHOSLOV. CHEM. COMM., vol. 37, 1972, pages 2059-2065, XP002176338 compound I,II,III page 2060 | 4,7,10, 17,23,24 |
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| X | A. GROUILLER ET AL.: "Novel p-toluenesulfonylation and thiocarbonylation of unprotected thymine nucleosides" SYNLETT, 1993, pages 221-222, XP002189351 compound 1 | 4,7,10, 17 |
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| X | E. WALTON ET AL.: "Branched-chain sugar nucleosides. V. Synthesis and antiviral properties of several branched-chain sugar nucleosides" J. MED. CHEM., vol. 12, 1969, pages 306-309, XP002189353 compounds 5,6,10,12,14,16-18 | 5,6,8,9, 11,12 |
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| X | HARAGUCHI K ET AL: "PREPARATION AND REACTIONS OF 2'- AND 3'-VINYL BROMIDES OF URACIL-NUCLEOSIDES: VERSATILE SYNTHONS FOR ANTI-HIV AGENTS" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 32, no. 28, 1991, pages 3391-3394, XP001041740 ISSN: 0040-4039 compounds 14,21 | 8,9 |
| X | S.N. MIKHAILOV ET AL.: "Substrate properties of C'-methyl nucleoside and C'-methyl-2'-deoxynucleoside 5'-triphosphates in RNA and DNA synthesis reactions catalysed by RNA and DNA polymerases" NUCLEOSIDES & NUCLEOTIDES, vol. 10, 1991, pages 339-343, XP001059775 compounds 3b,d,4b,d | 8,9,11, 12 |
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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X | T. IINO ET AL.: "Nucleosides and nucleotides. 139. Stereoselective synthesis of (2'S)-2'-C-alkyl-2'-deoxyuridines" NUCLEOSIDES & NUCLEOTIDES, vol. 15, 1996, pages 169-181, XP002189359 compound 9b | 8,11 |
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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| X | I.I. FEDEROV ET AL.: "3'-C-Branched 2'-deoxy-5-methyluridines: Synthesis, enzyme inhibition, and antiviral properties" J. MED. CHEM., vol. 35, 1992, pages 4567-4575, XP002189365 compounds 12-14,16,17,19 | 9,12 |
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| X | FR 2 662 165 A (UNIV PARIS CURIE) 22 November 1991 (1991-11-22) example 16 | 9 |
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Intr. National Application No

PCT/US 01/16687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X | K. HARAGUCHI ET AL.: "Stereoselective synthesis of 1'-C-branched uracil nucleosides from uridine" NUCLEOSIDES & NUCLEOTIDES, vol. 14, 1995, pages 417-420, XP002189369 compounds 17,18 | 10 |
| X | ALTMANN ET AL: "The synthesis of 1'-methyl carbocyclic thymidine and its effect on nucleic acid duplex stability" SYNLETT, THIEME VERLAG, STUTTGART, DE, no. 10, October 1994 (1994-10), pages 853-855, XP002105092 ISSN: 0936-5214 compound 1 | 10 |
| X | M. KAWANA ET AL.: "The deoxygenations of tosylated adenosine derivatives with Grignard reagents" NUCLEIC ACIDS SYMP. SER., vol. 17, 1986, pages 37-40, XP001059719 compound 13 | 11 |
| X | K. WALCZAK, E.B. PEDERSEN: "Synthesis of 1-(3-alkyl-2,3-dideoxy-D-pentofuranosyl)ur acils with potential anti-HIV activity" ACTA CHEM. SCAND., vol. 45, 1991, pages 930-934, XP002189370 compound 10c | 12 |
| X | H. USUI, T. UEDA: "Synthesis of 2'-deoxy-8,2'-ethanoadenosine and 3'-deoxy-8,3'-ethanoadenosine (Nucleosides and nucleotides. LXIV)" CHEM. PHARM. BULL., vol. 34, 1986, pages 15-23, XP002189371 compound 23 | 12 |
| A | US 5 977 061 A (DE CLERCQ ERIK DESIRE ALICE ET AL) 2 November 1999 (1999-11-02) column 1 -column 4 column 13, line 6 - line 28 | 1,130 |
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INTERNATIONAL SEARCH REPORT

Int ernational Application No

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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | LEYSEN P ET AL: "PERSPECTIVES FOR THE TREATMENT OF INFECTIONS WITH FLAVIVIRIDAE" CLINICAL MICROBIOLOGY REVIEWS, WASHINGTON, DC, US, vol. 13, no. 1, January 2000 (2000-01), pages 67-82, XP000889854 ISSN: 0893-8512 page 71, right-hand column -page 72, left-hand column ----- | 1,130 |
| A | WO 99 43691 A (CHOI YONGSEOK ;CHU CHUNG K (US); HONG JOON H (US); SHI JUNXING (US) 2 September 1999 (1999-09-02) the whole document ----- | 1,130 |
| E | WO 01 90121 A (NOVIRIO PHARMACEUTICALS LTD ;UNI DEGLI STUDI DI CAGLIARI (IT); LAC) 29 November 2001 (2001-11-29) the whole document ----- | 1-24 |

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 79-129 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,4,13-18,25-27 (in part),28,31,40-45,52,55,64-69,
76-78 (in part),79,82,91-96,103,106,115-120,
127-129 (in part),130,133,142-147,154,157,166-171,
178 (in part),180 (in part)

Compounds of Formula I of claim 1 or compounds of Formula IV of claim 4, pharmaceutical compositions and uses pertaining thereto.

2. Claims: 2,5,19-24,25-27 (in part),29,32,46-51,53,56,70-75,
76-78 (in part),80,83,97-102,104,107,121-126,
127-129 (in part),131,134,148-153,155,158,172-177,
178 (in part),179, 180 (in part)

Compounds of Formula II of claim 2 or compounds of Formula V of claim 5, pharmaceutical compositions and uses pertaining thereto.

3. Claims: 3,6,25-27 (in part),30,33,54,57,76-78 (in part),81,
84,105,108,127-129 (in part),132,135,156,159,
178 (in part),180 (in part)

Compounds of Formula III of claim 3 or compounds of Formula VI of claim 6, pharmaceutical compositions and uses pertaining thereto.

4. Claims: 7,25-27 (in part),34,58,76-78 (in part),85,109,
127-129 (in part),136,160,178 (in part),
180 (in part)

Compounds of Formulae VII or VIII or IX of claim 7, pharmaceutical compositions and uses pertaining thereto, where the compounds do not fall within one of the earlier described subjects.

5. Claims: 8,25-27 (in part),35,59,76-78 (in part),86,110,
127-129 (in part),137,161,178 (in part),
180 (in part)

Compounds of Formulae X or XI or XII of claim 8, pharmaceutical compositions and uses pertaining thereto, where the compounds do not fall within one of the earlier described subjects.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 9,25-27 (in part),36,60,76-78 (in part),87,111,
127-129 (in part),138,162,178 (in part),
180 (in part)

Compounds of Formulae XIII or XIV or XV of claim 9,
pharmaceutical compositions and uses pertaining thereto,
where the compounds do not fall within one of the earlier
described subjects.

7. Claims: 10, 25-27 (in part),37,61,76-78 (in part),88,112,
127-129 (in part),139,163,178 (in part),
180 (in part)

Compounds of Formula XVI of claim 10, pharmaceutical
compositions and uses pertaining thereto, where the
compounds do not fall within one of the earlier described
subjects.

8. Claims: 11,25-27 (in part),38,62,76-78 (in part),89,113,
127-129 (in part),140,164,178 (in part),
180 (in part)

Compounds of Formula XVII of claim 11, pharmaceutical
compositions and uses pertaining thereto, where the
compounds do not fall within one of the earlier described
subjects.

9. Claims: 12,25-27 (in part),39,63,76-78 (in part),90,114,
127-129 (in part),141,165,178 (in part),
180 (in part)

Compounds of Formula XVIII of claim 12, pharmaceutical
compositions and uses pertaining thereto, where the
compounds do not fall within one of the earlier described
subjects.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.:

7-12, 25-27, 34-39, 58-63, 76-78, 85-90, 109-114, 127-129, 136-141, 160-165, 178-180 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims. Consequently, the search has been restricted to the compounds of the above mentioned claims where R6 is methyl, ethyl, propyl, butyl, CF₃ or Br-vinyl. Furthermore, in the case where R6 is methyl for compounds XI, XIV, XVII, or XVIII of the above mentioned claims, only several documents were cited.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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